Reviews

PREVENTION

Myocardial Ischemia in Women: Lessons From the NHLBI WISE Study

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death for women. For almost 3 decades, more women than men have died from CVD, with the most recent annual statistics on mortality reporting that CVD accounted for 421 918 deaths among women in the United States. Although there have been significant declines in coronary heart disease (CHD) mortality for females, these reductions lag behind those seen in men. In addition, where there has been a decrease in mortality from CHD across all age groups over time in men, in the youngest women (age <55 years) there has been a notable increase in mortality from CHD. There are differences in the prevalence, symptoms, and pathophysiology of myocardial ischemia that occurs in women compared with men. In this paper, we review the pathophysiology and mechanisms of ischemic heart disease (IHD) in women, particularly focusing on what we have learned from the WISE study. We examine the sex-specific issues related to myocardial ischemia in women in terms of prevalence and prognosis, traditional and novel risk factors, diagnostic testing, as well as therapeutic management strategies for IHD.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death for women. For almost 3 decades, more women than men have died from CVD, with the most recent annual statistics on mortality reporting that CVD accounted for 421 918 deaths among women in the United States.[2] Although there have been significant declines in coronary heart disease (CHD) mortality for females, these reductions lag behind those seen in men. In addition, where there has been a decrease in mortality from CHD across all age groups over time in men, in the youngest women (age <55 years) there has been a notable increase in mortality from CHD.[3] There are differences in the prevalence, symptoms, and pathophysiology of myocardial ischemia that occurs in women compared with men.

Among many clinical cohorts, paradoxical sex differences have been observed in patients with signs and symptoms of CHD. Women have less anatomical obstructive coronary artery disease (CAD) and relatively more preserved left ventricular function despite higher rates of myocardial ischemia and mortality compared with men, even when controlling for age.[4–8] Data from the National Institutes of Health/National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE) study and other studies implicate adverse coronary reactivity,[9] microvascular dysfunction,[10] and plaque erosion/distal microembolization[11–13] as contributory to a female-specific myocardial ischemia pathophysiology. Thus, knowledge beyond an anatomical description of obstructive CAD may provide important clues to myocardial ischemia detection and treatment for women. For these reasons, the term ischemic heart disease (IHD) is more useful when discussing women and their form of CHD.[14]

In this article, we review the pathophysiology and mechanisms of IHD in women, particularly focusing on what we have learned from the WISE study. We examine the sex-specific issues related to myocardial ischemia in

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women in terms of prevalence and prognosis, traditional and novel risk factors, diagnostic testing, as well as therapeutic management strategies for IHD.

Ischemic Heart Disease Prevalence in Women

In addition to an absolute greater number of women dying from IHD, women have higher rates of death due to sudden cardiac death prior to hospital arrival compared with men.[15] There have been declines in mortality due to sudden cardiac death in men but little change in the death rates from this in women.[15] Women with IHD often have more persistent symptoms than men,[16] require more frequent hospitalizations, and report lower rates of general well-being in addition to limitations in their abilities to perform activities of daily living.[17,18] Despite the greater adverse outcomes seen in women with IHD at all ages, women have less-extensive and less-severe obstructive CAD, and better systolic function when compared with men.[7] Relatively higher CAD healthcare costs are incurred in women with IHD, as a result of (1) more frequent episodes of angina, resulting in increased office visits and hospitalizations; (2) higher myocardial infarction (MI) mortality; and (3) higher rates of heart failure hospitalization, as compared with men.[19,20]

This greater symptom burden and the higher rate of hospitalization and adverse outcomes in women compared with men, despite a lower prevalence and severity of anatomical CAD, poses a challenge for clinicians treating women with IHD.

Ischemic Heart Disease Risk Factors in Women

Traditional cardiac risk factors are highly prevalent in women, and many of these risk factors have either a greater impact or a higher prevalence, or both, in women. Women have higher cholesterol levels than men after their fifth decade of life.[21] An elevation in triglycerides is a more potent risk factor in women compared with men.[22–24] Obesity is more prevalent in women than men,[25] and a body mass index $\geq$40 kg/m^2 is associated with increased mortality in women.[26] Diabetes is also more prevalent in women, and diabetic women have at least a 3-fold greater risk of IHD than nondiabetic women, in addition to a greater mortality rate due to IHD when compared with diabetic men.[21,27–30] The metabolic syndrome, which is a cluster of cardiac risk factors (the combination of central obesity, glucose intolerance, hypertension, and dyslipidemia), is more common after menopause, likely related to hormonal-mediated changes.[31–33] Women with the metabolic syndrome are at the highest risk of developing IHD, compared with both men with metabolic syndrome and those without the metabolic syndrome.[34] The presence of traditional cardiac risk factors is important in the development of IHD, as >80% of women at midlife have $\geq$1 cardiac risk factors present,[21] and the presence of any cardiovascular risk factors increases the lifetime risk of developing IHD.[35,36]

Novel Risk Factors for Ischemic Heart Disease in Women

The Framingham Risk Score, which relies on traditional cardiac risk factors, can be used to predict the risk of IHD but often underestimates this risk in women.[37–39] Novel risk markers may improve detection in women. One such marker that may improve risk detection is high-sensitivity C-reactive protein (hsCRP).[40] It is consistently higher in women compared with men, from puberty onward.[41] Even with inflammatory diseases where hsCRP is elevated in both men and women, there is a 2- to 50-fold greater difference in hsCRP in women compared with men.[42] High-sensitivity CRP has also been shown to vary with levels of estrogen and other circulating sex hormones in postmenopausal women.[43] An elevation in hsCRP is associated with a greater risk of IHD than traditional risk factors would predict,[40,44] and its use in other scoring systems, such as the Reynolds Risk Score, has been proposed.[45] Other biomarkers (such as troponin I, N-terminal pro-brain natriuretic peptide, and cystatin C) may improve the assessment of risk of IHD.[46]

A unique risk factor for women are issues related to hormonal changes that can occur during a woman's lifetime. Ovulation dysfunction is one such unique risk factor, and it is associated with an increased risk of IHD and adverse CVD events. Functional hypothalamic amenorrhea, one cause of ovarian dysfunction, has been demonstrated to be associated with premature coronary atherosclerosis.[47] Polycystic ovarian syndrome is also associated with menstrual irregularities and is strongly associated with the presence of the metabolic syndrome and diabetes, and as a result of these issues, an increased risk of developing IHD.[48]

Issues that arise during pregnancy are also unique risk factors for IHD in women. Preeclampsia doubles the risk for subsequent IHD.[49] Gestational diabetes increases the risk of development of diabetes, and, therefore, IHD.[50]

Another risk factor for IHD to consider in women are the therapies used to treat breast cancer. Advancements in breast cancer treatment have led to improved survival but an elevated risk of IHD.[51] It remains unknown whether the elevated risk is entirely due to the specific therapies or due to the disease itself, which is also associated with some of the same risk factors that are related to IHD.

Symptoms and Prevalence of Myocardial Ischemia in Women

The evaluation of women with IHD is influenced by the definition of angina, given that "typical" symptoms have been established from largely male populations and reflect a pattern that is more typical in men.[52] Nonetheless, from a meta-analysis of 74 studies, it appears that women have a similar or even higher prevalence of angina compared with men.[53] In an analysis of 69 studies of symptoms with acute coronary syndromes (ACS), women did appear to have fewer "typical" symptoms compared with men, but the majority of women still had typical symptoms with their presentation.[54] Women with any symptoms suggestive of myocardial ischemia still have a probability of CAD that is lower than that for men,[55] and as the WISE study has demonstrated, 57% of women will not have obstructive CAD when coronary angiography is performed.[56] Indeed, these findings have been confirmed in larger data registries.[57] In those women without obstructive CAD, more than half will continue to have signs and symptoms of myocardial ischemia, be repeatedly hospitalized, and undergo repeat

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coronary angiography, all of which impacts healthcare resources.[19] From the WISE data, such women with chest pain and no obstructive CAD have a higher mortality and adverse cardiovascular events when compared with asymptomatic women, underscoring that the prognosis in women with symptoms and signs of ischemia is not benign, even when they have no obstructive CAD or "normal" coronary arteries.[58]

In women who present with ACS, it is not infrequent for the angiogram to be "normal" or demonstrate no obstructive CAD. Data from the National Cardiovascular Data Registry, which included 600 hospitals, showed that the odds for obstructive CAD were 50% lower for women compared with men.[7] Registries of ACS have demonstrated that nonobstructive CAD is more frequent in women compared with men, occurring in 10%–25% of women compared with 6%–10% of men.[59,60] In the setting of an ACS, "normal" coronary arteries do not have a benign prognosis.[60] Given the 1.4 million ACS events per year, 600 000 of which occur in women, this translates to 60 000–150 000 women with ACS and nonobstructive CAD. Despite less obstructive CAD, women have a poorer prognosis after an ACS, particularly younger women.[3,61] Although the worse prognosis in women has been attributed to advanced age and an increase in comorbidities,[5,6,62,63] in addition to an underutilization of lifesaving medication and therapies in women,[64] controlling for such variables still demonstrates persistent sex differences.[61,65]

Diagnosis of Myocardial Ischemia in Women

Exercise Stress Testing for Myocardial Ischemia in Women

An exercise stress test is often used to diagnose CAD. In women, the sensitivity and specificity of ST-segment depression are lower than in men,[66] but these values are influenced by the lower prevalence of obstructive CAD.[67] ST-segment depression is only one variable from exercise stress testing that has important diagnostic and prognostic value in women.[67] However, ST-segment depression can be combined with additional exercise stress-testing variables, including exercise duration and symptoms, to determine the Duke Treadmill Score, which more accurately predicts both the presence of CAD and IHD mortality in women.[68,69] In addition to other important prognostic markers, exercise capacity (fitness level) can be estimated using an exercise stress test, and an exercise capacity of <5 METs or the inability to achieve $\geq 85\%$ of age-predicted fitness level has been shown to be predictor of MI, IHD death, and all-cause mortality in women.[67,70,71]

Noninvasive Imaging for Myocardial Ischemia in Women

Imaging modalities can also be used to assess IHD risk in women, either in addition to exercise stress testing or with pharmacologic agents when exercise is not possible. Stress-induced regional wall-motion abnormalities and myocardial perfusion have relatively similar sensitivities and specificities for IHD in women.[66] Stress testing with echocardiography has somewhat lower sensitivity for detection of intermediate stenosis or single-vessel CAD, but its high negative predictive value makes this a particularly useful test to rule out IHD in younger women.[72] Myocardial perfusion can be evaluated in women using single-photon emission computed tomography (SPECT) imaging, positron-emission tomography, or cardiac magnetic resonance (CMR).

There is a large body of evidence relating to SPECT stress imaging showing that it effectively risk-stratifies women with suspected IHD.[72–74] In women with a normal myocardial perfusion study using SPECT imaging, the annual IHD event rate is very low (0.6%/y), in contrast to a much higher event rate (5%/y) in those with abnormal myocardial perfusion.[74] Certainly there are some limitations to SPECT imaging in women, including (1) reduced sensitivity as a result of severe multivessel disease, or as a result of diffuse endothelial or microvascular disease; (2) limited resolution, where smaller abnormalities are undetected due to a smaller heart; (3) breast attenuation; and (4) radiation exposure.[72] Another important issue for consideration when assessing the diagnostic accuracy of stress-imaging procedures that are "functional" assessments of the myocardium is the fact that the comparative gold standard of coronary angiography is an anatomic visualization of the coronary artery. A "false positive" stress-test result may be inappropriately labeled as such in women with objective symptoms of ischemia and resultant perfusion abnormalities.[65,75]

Stress CMR imaging is unique compared with other stress-imaging modalities, as it allows assessment of subendocardial perfusion. In a small study of 20 patients (80% female) with abnormal stress tests and normal coronary arteries, subendocardial ischemia was frequently present when compared with controls when adenosine CMR was performed.[76] This has been confirmed in another study,[77] whereas further publications have demonstrated both subendocardial and subepicadial ischemia in these patients.[78] In women with ACS and normal coronary arteries, subendocardial ischemia on CMR was the most common finding.[13] Newer techniques using CMR with exercise testing are being evaluated to assess IHD in women.[79] There is limited information regarding prognosis related to stress-induced CMR perfusion abnormalities in women with no obstructive CAD, but in a small substudy from WISE, women with nonobstructive CAD with an abnormal stress-induced CMR had an increase in adverse cardiovascular events.[75] Further investigations evaluating the prognostic value of subendocardial ischemia in women are needed.

Coronary Reactivity Testing for Myocardial Ischemia in Women

Vascular reactivity disproportionately affects women in a variety of other diseases, such as migraine headaches, Raynaud's phenomenon, and autoimmune arteritis.[14] It is not surprising that there would be an increased rate of vascular reactivity in the coronary circulation of women as well. In the past, coronary reactivity in women was thought to be due to vasospasm of the epicardial arteries, known as Prinzmetal's angina.[80] More recent research has revealed that microvascular coronary dysfunction (MCD) involving endothelial and nonendothelial pathways can be responsible for IHD in women, particularly in women with "normal" coronary arteries and those with nonobstructive CAD.[81]

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Microvascular Coronary Dysfunction: There is emerging data supporting a gender-specific role of MCD, as an early stage of IHD. Autopsy data has shown that women have more coronary plaque erosion and distal embolization compared with men.[11] In addition, microvascular disease characterized by retinal artery narrowing is associated with CVD events in women but not men.[10,82] Other sex differences, including smaller arterial size and more prominent positive remodeling, may result in more MCD in IHD in women. In the WISE study, almost half of the women who had measures of coronary flow reserve had abnormal responses consistent with MCD.[83] In another study that examined intravascular ultrasound and coronary reactivity testing in men and women, women had far less obstructive CAD and more MCD than men.[84] This evidence of MCD appears to be part of the IHD pathophysiology, and may explain the higher rates of angina in women, in addition to the ischemia and ACS in absence of obstructive CAD that occurs so frequently in women.

Endothelial Dysfunction: Endothelial response is adversely affected by traditional cardiac risk factors, including tobacco abuse, hyperlipidemia, diabetes, and hypertension,[85] and worsens after menopause.[86] Endothelial dysfunction can contribute to IHD in women. Both peripheral assessment of endothelial response and direct assessment of endothelial function in the coronary circulation have been shown to be associated with IHD risk.[5] Restoration of endothelial function has been demonstrated to improve outcomes in women, as seen in a group of postmenopausal, hypertensive women who were treated for hypertension and who also had an improvement in their endothelial response.[87]

Both MCD (non–endothelial dependent) and endothelial dysfunction (endothelial-dependent) predict adverse cardiovascular events.[88] The role of MCD in IHD among women without obstructive CAD has only recently been recognized, and more complete assessment of coronary reactivity in such a setting has been suggested.[58,89]

Treatment and Outcomes of Obstructive Coronary Artery Disease in Women

Optimal medical therapy for women with IHD is no different than for men, but women often receive less intensive medical therapy or lifestyle counseling, which ultimately influences outcomes.[16,64,90–92] There are also sex differences in treatment for ACS that also influence outcomes. In addition to the difference in medical therapy, there are sex differences in the use of cardiac catheterization and revascularization use and timing, which are associated with poorer outcomes in women after ACS or MI.[64,91]

There are some sex differences regarding invasive strategies with ACS. In a meta-analysis of 8 ACS trials, an invasive strategy resulted in a reduction of the composite endpoint of death, MI, or repeat ACS in both sexes, but it was more beneficial in women with positive biomarkers (33% risk reduction) in contrast with women with negative biomarkers, where an invasive strategy was not associated with a significant reduction in the composite endpoint.[93] Any such difference based on biomarkers was not seen in men. Women have also been shown to have a higher mortality than men with percutaneous coronary intervention after ST-elevation and non–ST-elevation MI.[94] In contrast, the use of fibrinolysis has demonstrated that in women there is a lower incidence of mortality or nonfatal MI at 30 days, compared with men who received enoxaparin compared with unfractionated heparin, suggesting that specific therapies may beneficially impact outcomes in women.[95]

There have been studies documenting increased bleeding risk in women undergoing percutaneous coronary intervention who receive glycoprotein IIb/IIIa inhibitors, but adverse events showed no sex differences.[96] In a meta-analysis of ACS populations, whereas men benefited from glycoprotein IIb/IIIa inhibitors, women experienced more harm.[97] Nonetheless, high-risk women with troponin elevations did demonstrate a benefit. Prior studies have suggested that the elevated bleeding risk in women is due to body size and renal function,[90] and studies have shown that the sex difference in bleeding resolves when doses were adjusted for age and renal function.[96]

There remains a persistent pattern of higher mortality and poorer cardiovascular outcomes in women compared with men with IHD,[16,61,91] which is most likely attributable to suboptimal treatment of women despite proved obstructive CAD. This is occurring despite evidence showing that application of guideline therapy post-ACS is able to reduce the mortality gap seen in women.[92] This is also occurring despite the strong evidence that management of CAD and chronic angina with intensive medical therapy benefits both sexes equally.[98]

Treatment and Outcomes of Nonobstructive Coronary Artery Disease in Women

The prognosis for those with "normal" coronary arteries, in the setting of signs and symptoms of myocardial ischemia, was initially reported as benign,[99,100] but more recently there is increasing evidence showing that this is not a benign condition and the risk of cardiovascular events is higher when compared with asymptomatic women.[19,58] In those with ACS and no obstructive CAD, there was a 2% risk of death and MI at 30 days post-MI.[101] In symptomatic women with "normal" coronary arteries and evidence of myocardial ischemia who had evidence of endothelial dysfunction, there was a greater risk of developing obstructive CAD in the following 10 years.[102] In the WISE study, we have shown that the 5-year CVD event rate for symptomatic women with evidence of myocardial ischemia and mild CAD (1%–45% stenosis) was 16%, compared with 7.9% for women with no coronary stenosis, in contrast with a rate of 2.4% in asymptomatic women who were age- and race-matched ($P \leq 0.002$).

Most of the treatment for nonobstructive CAD in women has focused on improvement of symptoms or vascular-function response. Beta-blockers appear to improve symptoms, whereas calcium channel blockers have been shown to be ineffective.[103,104] Statins and angiotensin-converting enzyme inhibitors (and a combination of both) have been shown to improve endothelial dysfunction and may improve symptoms and outcomes.[105–107] Exercise training in such women has been demonstrated to improve symptoms and improve exercise capacity.[108] The use of

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imipramine may have a role in women with normal coronary arteries, as it appears to improve symptoms through a visceral analgesic effect.[109] L-arginine also has been proposed to improve endothelial function in those with symptoms and nonobstructive CAD,[110,111] but concerns have been raised regarding its safety.[112] A recently published pilot study in women with angina, myocardial ischemia, and nonobstructive CAD showed that ranolazine improves angina, particularly in those with documented microvascular dysfunction.[113] At this point, there are no randomized trials comparing risk reduction and medical therapies for this complicated but highly prevalent issue. Future research will be needed to determine optimal treatment for such women, assessing not only improvements in symptoms and microvascular function, but also effect on prognosis.

Conclusion

Myocardial ischemia has specific sex differences. Despite a lower prevalence of obstructive CAD in women, women have a higher prevalence of symptoms, ischemia, and mortality relative to men. Traditional and novel risk factors can help in the identification of at-risk women. Diagnostic testing can be used to accurately assess for myocardial ischemia in symptomatic women, in addition to providing important prognostic information. The frequent occurrence of symptoms of angina, evidence of myocardial ischemia in the absence of obstructive CAD associated with MCD, and endothelial dysfunction measured by coronary reactivity testing suggest a sex-specific pathophysiology of IHD in women.

Currently, the treatment of women with IHD is less aggressive than for men, which continues to translate to poorer outcomes for women after ACS, and, in women with persistent chest pain syndromes, more downstream expenditures. The optimal treatment for symptomatic women with myocardial ischemia with no obstructive CAD is still being determined, but assessment of coronary reactivity should be considered as part of the evaluation of women who have symptoms and signs of ischemia without obstructive CAD.

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